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TITLE: A Randomized Study of the Effects of Tibolone on Bone Density, Menopausal Symptoms, and Breast Density in High-Risk Women After Prophylactic Oophorectomy

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13. ABSTRACT (Maximum 200 Words) The synthetic steroid tibolone has been shown to improve bone mass, mitigate menopausal symptoms and reduce breast density in women with natural menopause. It has not been evaluated in an abrupt menopause model, as occurs in women at high risk of breast cancer because of inherited risk who undergo prophylactic oophorectomy to reduce breast cancer risk. We will conduct a double-blind randomized placebo-control trial to test the hypotheses that Tibolone will accomplish these goals in high-risk premenopausal women undergoing prophylactic oophorectomy, and provide an alternative for them to manage menopause symptoms without increasing breast cancer risk. Our progress to date has been: <ol style="list-style-type: none"> 1. Completion of the development and institutional IRB approval of the research protocol, recruitment and study management materials 2. Development and piloting of algorithms for symptom management; training of research nurses to use them for management of patients with menopause symptoms and breast cancer or breast cancer risk 3. Tibolone and placebo are obtained. The protocol is ready for initiation after DAMD Human Subjects approval 4. We have developed systems for patient accrual working with gynecologic oncologists in involved institutions In summary, we are ready to begin subject recruitment as soon as we receive DAMD approval to proceed.				
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INTRODUCTION

Women with germline *BRCA1* and *BRCA2* mutations face a lifetime risk of breast cancer of 36-87%, as well as high risks of ovarian cancers, approximately 40% and 20%, respectively. Women who test positive for deleterious *BRCA1/2* mutations are advised to undergo frequent cancer screening and to consider prophylactic surgery. In particular, prophylactic bilateral salpingo-oophorectomy is recommended for premenopausal women because of strong data demonstrating not only a reduction in ovarian cancer risk exceeding 90% in the face of ineffective early detection strategies, but also reduction in breast cancer risk of approximately 50%. However, the optimal timing of surgery is debated, since oophorectomy induces premature menopause, with all of the implications of early estrogen deficiency, including an increased risk of osteoporosis and vasomotor symptoms. Hormone replacement therapy has been shown to increase breast cancer risk in the general population, creating a difficult dilemma for young mutation carriers who undergo surgery to improve survival, but often at a significant cost in quality of life. In this project, we are evaluating the agent Tibolone, a synthetic steroid with an attractive safety and efficacy profile, for its ability to prevent bone loss, mitigate menopause symptoms, and modulate breast density in high risk women following prophylactic oophorectomy. We hope to provide these women with a safe and effective alternative for management of menopause symptoms and consequences after risk-reducing prophylactic surgery.

BODY

Task 1. Finalize protocol implementation (year 1):

- a. Reformat identified instruments into a single packet of forms with more uniform appearance and improved data entry capacity (data collection forms created, database preparation). **Instruments have been designed for data collection and databases constructed for central data management at the Quality Assurance for Clinical Trials center at Dana Farber; study procedures have been completed for data collection at both institutions; study nurses have been trained in the use of menopause symptom management algorithms in order to permit comparison of symptoms and standardized data collection at all sites.**
- b. Finalize protocol implementation at two cooperating institutions. **The protocol has been approved for the institutions; the labs prepared; the study staff trained; the data collection systems established, and recruitment strategies ready to begin as soon as DAMD human subjects review and investigator response to the review (revision as indicated) are complete.**

Task 2. Recruitment of study participants (Year 2)

- a. Enroll women with *BRCA1/2* mutations from two clinical cancer genetics clinics who are unaffected with cancer, are premenopausal, and who plan prophylactic mastectomy within 2 months of signing consent to participate. **Participating sites continue to identify new women with germline mutations who are undergoing prophylactic oophorectomy who will comprise the potential study population for**

this trial. The gynecologic oncology surgeons have been made aware of the trial and are prepared to refer women to the study. Systems for consenting and enrolling perspective participants are ready.

- b. At surgery, provide consenting patients with transdermal estrogen and oral progesterone for two months. **The protocol has been modified to permit women to use the hormone replacement regimen their provider prefers for the time in which they are permitted hormone supplementation.**

Task 3. Obtain study measurements at specified intervals: baseline, 6 months and 12 months.

No work has been done on this task

- a. Obtain bone mineral density and markers of bone turnover at baseline (end of hormone replacement), 6 months and 12 months on medication
- b. Obtain baseline and 12 month mammograms from all sites. Batched mammograms will be collected for digitization and breast density calculation
- c. Collect baseline menopause symptom data using standardized instruments
- d. After 2 months without adjuvant medications, add agents intended to mitigate menopause symptoms in specified manner, measuring menopause symptoms on these additional agents.

Task 4. Data analysis, manuscript preparation

No work has been done on this task

- a. Data for the three specific aims will be entered, cleaned and analysed
- b. Manuscripts will be prepared addressing the 3 specific effects of tibolone compared to placebo: bone, menopause symptoms and mammographic breast density.
- c. The final report will be prepared.

KEY RESEARCH ACCOMPLISHMENTS:

- We have developed and obtained institutional IRB approval of the research protocol, recruitment and study management materials;
- We have developed and piloted algorithms for symptom management, trained research nurses to use them for management of patients with menopause symptoms and breast cancer or breast cancer risk;
- We have obtained Tibolone and placebo. The protocol is ready for initiation after DAMD Human Subjects approval.
- We have developed systems for patient accrual working with gynecologic oncologists in involved institutions.

REPORTABLE OUTCOMES:

Not applicable

CONCLUSIONS:

To date, we have developed the protocol for conduct of the study, as well as all pertinent recruitment and data collection materials, and have trained the study nurses. We are looking forward to proceeding with implementation of the protocol as soon as we revise our materials in accordance with DAMD suggestions and required changes so can begin the trial.

REFERENCES:

Not applicable

APPENDICES:

Not applicable